Systemic Versus Intracoronary Streptokinase Infusion in the Treatment of Acute Myocardial Infarction

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Clinically encouraging results can be obtained with an intravenous high dose short-time infusion of streptokinase in patients with evolving myocardial infarction. The feasibility and efficacy of the intracoronary and the systemic approach of streptokinase therapy in acute myocardial infarction are discussed in this report and include topics such as infarct artery recanalization success rate, coronary thrombus lysis time, benefit for patients with subtotal coronary occlusion, reocclusion rate, the necessity of additional surgical interventions, salvage of ischemic myocardium and side effects.

The value of high dose intravenous short-time streptokinase infusion needs to be assessed with properly designed clinical trials against the background afforded by the results observed with direct intracoronary streptokinase infusion.

New dimensions and perspectives of clinical interest emerged since coronary angiography reestablished the importance of coronary thrombosis as the major precipitating event in the pathogenesis of acute myocardial infarction (1). Rapid thrombolysis with attendant recanalization and reperfusion was achieved with the use of intracoronary infusion of streptokinase, thereby producing possible salutary results of salvaging jeopardized ischemic myocardium, reducing infarct size and improving left ventricular function (2–5). However, introducing this mode of therapy for all patients would imply staffing an overwhelming number of catheterization laboratories 24 hours a day, 7 days a week with appropriately trained personnel. Therefore, the recent observation that systemic infusion of streptokinase also rapidly lyses coronary occluding thrombi in patients with acute myocardial infarction calls for a reassessment of the intravenous route as initial therapy (6–9).

In this report, recent data with high dose intravenous short-time infusion are discussed, thereby comparing feasibility and efficacy of the intracoronary and systemic approaches to streptokinase therapy in acute myocardial infarction.

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Randomized Clinical Trials With Intravenous Streptokinase Infusion

In 1959, Fletcher et al. (10) were the first to use an intravenous streptokinase infusion in the treatment of acute myocardial infarction. They suggested that patients may derive clinical benefit from this treatment and gave considerable assurance that certain theoretical objections that could be raised against this mode of therapy were without practical basis. Since 1959, 15 prospective randomized placebo controlled clinical trials have been carried out. In most of the trials, a loading dose of 250,000 IU streptokinase was followed by an infusion of 100,000 IU/h for 12 to 24 hours (11,12). Despite these doses, bleeding complications were no major problem as a cause of death, although they were observed slightly more frequently than in the control group (11). Of the 2,467 patients treated with streptokinase in 12 multicenter studies, 6 patients died from bleeding complications related to the thrombolytic therapy (13). The rate of cardiac rupture was found to be similar in both the treatment and control groups. A true deleterious effect of thrombolytic treatment or a significant difference in favor of the control group has never been reported (11).

Results of treatment within 12 hours. In Table 1, data on the six trials in which intravenous streptokinase infusion was initiated within 12 hours after onset of symptoms are presented (6). In five trials, a significant reduction in death among treated patients as compared with untreated patients was claimed. In four trials, the mortality rate in the control group appeared to be relatively high; however, at that time

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Table 1. Data From Six Prospective Randomized Trials With Intravenous Streptokinase (SK) Infusion Within 12 Hours After Onset of Symptoms in Patients With Acute Myocardial Infarction

Trials (Ref)	Year	Patients (n)	Dose (IU)		Duration (h)	Mortality (%)		Follow-up (days)	Significance
			Initial	Per Hour		SK	Control		
German-Swiss I (14)	1966	558	250,000	166,000	18	14.1	21.7	40	$p < 0.05$
German-Swiss II (15)	1971	269	250,000	137,000	18	14.5	26 0	40	$p < 0.01$
Italian (16)	1971	321	250,000	150,000	12	11 6	11.5	40	NS
Frankfort (17)	1973	206	250,000	200,000	3	12.8	27.6	40	$p < 0.01$
Austrian (18)	1977	728	500,000	110,000	20	10.5	17.3	40	$p < 0.01$
European Cooperative (19)	1979	315	250,000	100,000	24	15.6	30.6	180	$p < 0.01$

n = number; NS = not significant, p = probability; Ref = reference

the mortality rate in patients with acute myocardial infarction was generally higher than today. In the most recent well designed trial of the European Cooperative Study Group (19), low risk patients were excluded, which in part may explain an overall mortality rate within 6 months of 30.6% in the control group. The difference in the mortality rate up to the 21st day was not statistically significant in this trial; mortality rate was 11.5% in the group treated with streptokinase and 17.6% in the control group.

Early treatment within 3 hours after onset of symptoms was suggested as more favorable than later treatment (17,20); however, a clear significance has never been demonstrated (11). In the European Cooperative Study Group trial, only two patients had been treated within 3 hours and about one-third 3 to 5 hours after the onset of symptoms. There was a consistent difference in the mortality rate of the two groups that had received treatment within 12 hours after the suggested beginning of myocardial infarction (19).

Limitations of studies. Although these results seemed encouraging, for various reasons intravenous thrombolysis did not become a generally accepted mode of therapy in acute myocardial infarction (21,22). Because of erroneous design, inaccurate technology or failure of appropriate data analysis, most of the earlier studies (11,12) remained equivocal; however, the true impact of the European Cooperative Study Group trial (19) was also disputed, mostly because the mechanism of the beneficial effect remained an unanswered major question. At the time, rapid lysis of thrombotic coronary occlusion had not been proved and the suggestion that an improvement in microcirculation through a reduction in total peripheral resistance may limit the infarct size and thus reduce mortality did not seem very attractive. It was claimed that there were safer and more easily controlled means of reducing afterload than by using a 12 to 24 hour infusion of streptokinase with its bleeding hazards (22).

Recanalization Success Rate

Intracoronary streptokinase therapy. Recanalization success rates between 64% (23) and more than 90% (5) have been reported for intracoronary streptokinase infusion. These results are difficult to judge, however, partly because an attempt at mechanical recanalization was made, nitroglycerin or nifedipine was administered by intracoronary injection and in some patients the occluded coronary artery was opened by the intracoronary injection of contrast material (24). Recanalization of 276 (76%) of 361 totally occluded infarct arteries was reported in the European Reperfusion Registry (25). A special coronary infusion catheter, advanced through the lumen of the angiography catheter to a point 2 to 3 mm proximal to the site of coronary occlusion, may improve the success rate (5).

Apparently, the interval between the onset of symptoms and the initiation of streptokinase therapy is of major importance (26,27). Recent investigations by Lee et al. (28) showed that when an intracoronary streptokinase infusion was begun less than 5 hours after onset of symptoms, recanalization was achieved in 18 of 22 totally occluded infarct vessels; however, recanalization was successful in only 13 patients (59%) within 1 hour after starting treatment. With initiation of intracoronary streptokinase infusion 5 to 7 hours after the onset of symptoms, a 1 hour success rate in 4 (37%) of 11 patients was achieved.

Intravenous streptokinase therapy. With a 30 minute intravenous infusion of 500,000 IU streptokinase, we could angiographically prove reopening of 8 of 15 (6) or 11 of 21 (29) totally occluded coronary infarct vessels within 1 hour. These recanalization success rates refer to starting treatment 3.8 ± 1.3 hours (± standard deviation) after symptom onset. The success rate was significantly dependent on the time interval from symptom onset to treatment.

This may partly explain the higher efficacy reported with intracoronary streptokinase infusion. All our patients receiving streptokinase within 3 hours after the onset of symptoms had restoration of coronary blood flow (30).

Neuhaus et al. (31) demonstrated reopening of a totally occluded coronary artery within 35 to 80 minutes in 24 (63%) of 38 patients by a 1 hour intravenous infusion of approximately 1,500,000 IU streptokinase. In this study, successful recanalization was also closely related to a shorter interval from the onset of symptoms to initiation of streptokinase therapy. On the average, infusion was initiated 3.2 hours after the onset of symptoms; there was a success rate of 73% in patients treated within 3 hours after symptom onset.

Without coronary angiography in the acute phase, we recently studied the effects of an intravenous streptokinase infusion in 50 patients with acute transmural myocardial infarction by means of serial serum creatine kinase (CK-MB) activity curves and angiography in the fourth week (29). Nineteen patients received 500,000 IR streptokinase within 30 minutes and 31 received 1,500,000 IU within 1 hour. For comparative purposes, the angiographic findings obtained approximately 8 weeks after the acute event in 52 patients without streptokinase or heparin treatment were evaluated (Table 2). In the group treated with streptokinase, the involved coronary artery corresponding to the electrocardiographic location of myocardial injury was found patent in 84% as compared with 25% in the control group.

Furthermore, in contrast to the group treated with streptokinase, the control group patients with nonoccluded infarct vessels often had remaining subtotal arteriosclerotic obstruction with threadlike distal coronary patency only. Comparable findings in patients without streptokinase treatment were recently reported by Pichard et al. (32). Thus, spontaneous clot lysis with substantial persisting recanalization does not occur for a period of at least 1 to 2 months after transmural myocardial infarction. Patients without streptokinase treatment had total occlusion of the infarct vessel 1 to 2 months after acute myocardial infarction at a similar frequency as that in patients with evolving acute myocardial infarction who presented for streptokinase therapy (26,29).

The high recanalization success rate as well as the importance of expeditious intravenous streptokinase infusion are also demonstrated by the results listed in Table 3. Of a total of 75 patients, 6 with postintervention reinfarction were excluded. In the remaining 69 patients, the infarct-related coronary artery was found patent in the fourth week in all 36 patients in whom intravenous streptokinase infusion was started within 3 hours after the onset of symptoms, and in 27 (82%) of 33 with initiation of treatment more than 3 hours after symptom onset (29).

Conclusion. Rapid restoration of coronary blood flow is closely related to a shorter interval from symptom onset to intravenous streptokinase infusion; however, ultimate clot lysis most probably occurs as frequently with the intravenous approach as with intracoronary application.

Thrombus Lysis Time

Intravenous streptokinase. It has been shown that lysis of a coronary clot with the intravenous approach lasts, on the average, 15 minutes longer than with intracoronary streptokinase application (8,31). The study by Neuhaus et al. (8), however, was not performed in a random fashion; thus the data obtained are not firmly conclusive. During an observation period of 60 to 80 minutes, the rate of recanalization with the intravenous approach was somewhat lower than that reported for intracoronary streptokinase application. As discussed previously, restoration of coronary blood flow takes place in nearly all patients with acute myocardial infarction treated with intravenous streptokinase infusion, but may occur with a delay of up to a few hours. Thus, the difference in the total average lysis time between both modes of streptokinase infusion may be more than 15 minutes. Nevertheless, the delay in restoration of coronary blood flow with the intravenous approach as compared with intracoronary streptokinase infusion may not be of decisive importance, especially when considering that systemic streptokinase infusion can be readily implemented early by the primary care physician in the mobile coronary care unit or even in the patient's home (30). This results not only in avoiding loss of time until angiography but also, because of earlier initiation of treatment, in a shorter thrombus lysis time. An early appearance of creatine kinase-MB in the

Table 2. Residual Mean Diameter Stenosis of the Infarct-Related Coronary Artery in Patients With and Without Intravenous Streptokinase (SK) Therapy

Diameter Stenosis of the Infarct Artery	4th Week, SK	3 to 13 Weeks, No SK
< 55%	9 (18%)	1 (2%)
55 to 69%	20 (40%)	1 (2%)
≥ 70%	13 (26%)	11 (21%)
Occluded	8 (16%)	39 (75%)
Total	50	52

Table 3. Relation Between Beginning of Intravenous Streptokinase Infusion Within 3 Hours or More After Onset of Symptoms and Patency of the Infarct Coronary Artery in the Fourth Week (69 patients without postintervention reinfarction)

	≤ 3 h	> 3 h	Total
Patent	36	27	63
Occluded	0	6	6
Total	36	33	69
Risk	0%	18.2%	

Chi-square $\chi^2 = 7.17$, $p < 0.01$

systemic circulation and a premature peak in the serial serum enzyme curve together with rapid electrocardiographic changes strongly suggest that in the majority of these patients, restoration of coronary blood flow is achieved within 1 to 2 hours after beginning the intravenous streptokinase infusion (30).

Combined intravenous and intracoronary streptokinase. Most rapid recanalization after onset of symptoms can probably be achieved by a combination of both modes of streptokinase application (29). With an initial 20 minute intravenous infusion of 200,000 IU streptokinase, the recanalization success rate during a subsequent intracoronary streptokinase application could be improved from 81 to 91% and the thrombus lysis time from the beginning of the intracoronary application shortened from 35 ± 19 to 18 ± 9 minutes (33). Similarly, immediate institution of an intravenous infusion of 30,000 IU streptokinase/min resulted in a patent artery in 45% of patients on angiography 30 to 60 minutes later; the additional intracoronary streptokinase application led to a rapid recanalization in more than 80% of the patients (34).

Conclusion. Thrombus lysis time lasts longer with intravenous streptokinase infusion as compared with intracoronary application; however the difference may be of minor importance in the usual clinical setting of acute myocardial infarction.

Patients With Subtotal Occlusion

Objections against intravenous streptokinase treatment without angiography in the acute phase are based on the concern that patients will be treated who do not have complete coronary artery occlusion. DeWood et al. (1) observed patent coronary arteries in only 13% of the patients studied with angiography within 4 hours but in 32% of the patients 6 to 12 hours after the onset of symptoms, suggesting some spontaneous recanalization after the very early hours of evolving myocardial infarction. However, most of the patent arteries remained so highly obstructed that it is questionable if there was sufficient nutritional flow. According to our experience, these patients may benefit most from restoration of a sufficient coronary flow when intravenous streptokinase infusion dissolves the threatening coronary thrombus. In four patients, we found an increase in ejection fraction from 49.5 ± 12.3% before intervention to 60.6 ± 0.4% in the fourth week while the systolic segmental shortening of the ischemic area improved from 5.9 ± 9.3 to 26.7 ± 7.7% (30). On videodensitometry, an improved coronary flow could be demonstrated after intravenous streptokinase infusion (35). The presence of nonoccluding coronary thrombus in unstable myocardial ischemic syndrome (36) that can progress to total occlusion and myocardial infarction is consistent with the potential spectrum of propagating thrombus extending to occluding thrombosis in acute myocardial infarction. Neill et al. (37) have shown that approximately one-third of patients with intermediate coronary syndrome exhibit late total occlusion of a previously highly stenotic lesion, frequently with associated myocardial infarction. In patients with unstable angina pectoris, it was shown that intravenous streptokinase infusion can prevent progression to myocardial infarction (38).

Conclusion. Different mechanisms are involved in patients with acute myocardial infarction but incomplete occlusion of the infarct-related artery. Nonoccluding thrombosis is most probably a major component. These patients may benefit most from immediate intravenous streptokinase infusion.

Reocclusion Rate and Need for Additional Surgical Intervention

In the majority of cases, a significant arteriosclerotic stenosis at the site of the previous thrombotic occlusion remains after successful streptokinase treatment. Thus, it can be assumed that the affected coronary artery continues to pose the same hazard after streptokinase-induced restoration of coronary blood flow that it posed before thrombolytic occlusion. Therefore, early mechanical interventions such as coronary artery bypass grafting and percutaneous transluminal coronary angioplasty have been performed in suitable patients (39–41); however, the necessity and efficacy of such additional interventions remain to be determined. The finding that improvement in ventricular function was independent of whether the bypass graft circumventing the residual fixed arteriosclerotic stenosis in the infarct vessel was patent or not may indicate that early reperfusion achieved by the streptokinase-induced recanalization alone was sufficient to restore considerable myocardial function in evolving myocardial infarction (39).

Reinfarction and late reocclusion rate. Although a high incidence rate of reinfarction (21%) and late hospital reocclusion (8%) has been reported after successful intracoronary streptokinase treatment (42), this is not the general experience. Evidence was provided (5) that continued intracoronary streptokinase infusion for at least 60 minutes after the artery had become patent substantially lowers the incidence of reocclusion. Furthermore, late reocclusion is usually either not associated with reinfarction or the clinical course of reinfarction is mild and the corresponding increase in the CK-MB serum activity is small, possibly because of interim development of improved collateral circulation (30,43).

With the intravenous approach, the reocclusion or reinfarction rate, or both, was less than 10% (29,31). Rutsch (33) observed a decrease in reinfarction rate from 13 to 7% since intracoronary streptokinase application was preceded by an intravenous streptokinase infusion (33). However, probably more important for preventing reinfarction is proper

poststreptokinase anticoagulation with a total dose of heparin of more than 20,000 IU/day for at least 3 to 5 days, replaced by phenprocoumon or warfarin thereafter.

Indications for additional intervention. The decision if and in which patient additional mechanical intervention should be undertaken can be made without angiography preceding the streptokinase treatment. After early intravenous streptokinase infusion, coronary angiography can be performed on an elective basis and in relation to the clinical course. Even immediately after or during intravenous streptokinase infusion, angiography can be performed safely (33,34). For an early surgical intervention systemic thrombolytic activity could be stopped with epsilon-amino-capronic acid and aprotenin.

Conclusion. Performance of intravenous streptokinase infusion without preceding angiography in patients with acute myocardial infarction does not limit the possibility of applying appropriately subsequent surgical or mechanical intervention.

Salvage of Ischemic Myocardium

Assessment of left ventricular function by means of repeated angiography (24,44), cardiac gated blood pool imaging (45) or thallium-201 studies (46–48) revealed enhanced global and regional left ventricular performance compared with prestreptokinase left ventricular function in patients with recanalization of an occluded infarct artery, whereas such improvement was absent in nonrecanalized patients. The same results were found in patients treated with a high dose intravenous short-time infusion of streptokinase (7,31). In patients with reopening of the involved coronary artery, systolic segmental shortening improved significantly from 7.0 ± 4.9 before intervention to 20.1 ± 10.3 in the fourth week after acute myocardial infarction (30).

Ventricular wall motion studies after intravenous streptokinase. Recently, we studied regional left ventricular wall motion abnormalities in patients who had received an intravenous streptokinase infusion without angiography in the acute phase using angiography in the fourth week (29). Patients with previous infarction or postintervention reinfarction were excluded. There was a significant inverse correlation between the percent of segmental systolic shortening of the infarcted area and time interval from symptom onset to treatment; that is, the infarct size calculated in the fourth week significantly depended on treatment delay (Fig. 1). Segmental area shortening of 10% or less was defined as akinetic. Patients treated within 3 hours after the onset of symptoms exhibited significantly less akinesia than did patients with initiation of intravenous streptokinase infusion 3 to 6 hours after the onset of symptoms (Table 4). These data again strongly suggest that at least in those patients treated early, jeopardized myocardium was preserved by early restoration of coronary blood flow during the acute stage of myocardial infarction.

Table 4. Relation Between Beginning of Intravenous Streptokinase (SK) Infusion Within 3 Hours or More Than 3 Hours After Symptom Onset and Findings of Akinetic Segments of the Left Ventricular Wall in the Fourth Week (34 patients without previous infarction or postintervention reinfarction)

	≤ 3 h	> 3 h	Total
No akinesia	11	4	15
Akinesia	6	13	19
Total	17	17	34
Risk	35.3%	76.4%	

Chi-square (χ^2) = 5.85; $p < 0.05$.

Conclusion. Patients with acute myocardial infarction may benefit from an intracoronary as well as an intravenous streptokinase infusion. The efficacy of both modes of intervention on myocardial salvage and restoration of function, however, has not been evaluated objectively because of lack of an untreated randomized control group in all studies.

Side Effects

Streptokinase therapy. With preceding intravenous injection of corticosteroids, no serious pyretic or allergic reaction attributable to streptokinase occurred. With an intravenous short-time infusion of 500,000 to 1,500,000 IU streptokinase in more than 100 patients, there were no serious bleeding complications, although serum fibrinogen concentrations declined below 1 g/liter over a period of 27 hours (29,31). Systemic fibrinolytic activity with major decrease of fibrinogen concentration is also common with intracoronary streptokinase infusion. In 204 patients treated with intracoronary streptokinase infusion in four German clinics, the incidence of serious systemic hemorrhagic complications requiring blood transfusion was 7.4% (42). Intracerebral hemorrhage occurred in one patient who died of cardiogenic shock (26).

Cardiac catheterization. Coronary angiography, a prerequisite for intracoronary streptokinase application, is not without its complication in the setting of acute myocardial infarction. DeWood et al. (1) quoted a 9.3% rate of ventricular fibrillation. During catheterization and attempted recanalization of an occluded artery, ventricular fibrillation in 7 of 41 patients has been reported (24). In the study of Serruys et al. (23), 5 of 83 patients died during the catheterization procedure, 2 of them because of migration of thrombotic material. Of the 62 surviving patients, 21 had complications that required treatment. Complications such as ventricular tachyarrhythmias or substantial decrease in arterial blood pressure may cause additional damage to jeopardized ischemic myocardium.

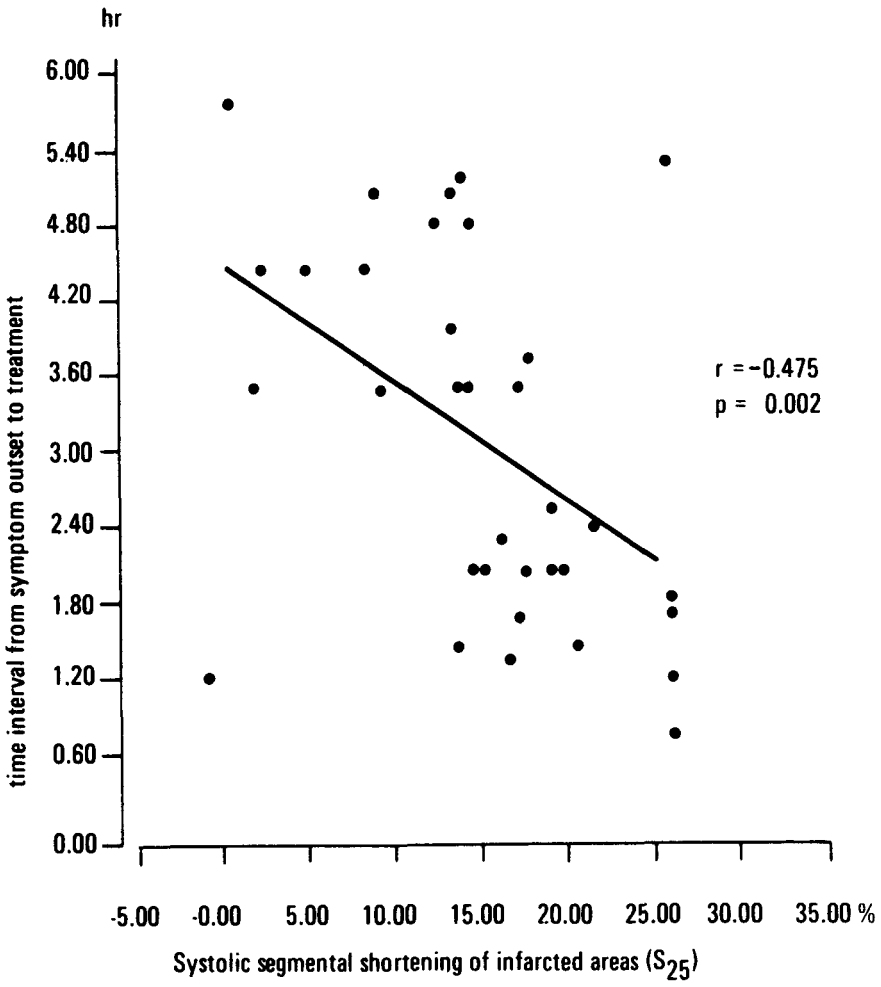

Figure 1. Relation between time interval from onset of symptoms to commencement of intravenous streptokinase infusion and local left ventricular contraction disorders during the fourth week in 34 patients without previous infarction or postintervention reinfarction. In five patients with a segmental systolic shortening greater than 25%, the value was listed as 26%.

Conclusion. With both modes of streptokinase treatment, the incidence of serious systemic hemorrhagic complications seems to be low. Cardiac catheterization in acute myocardial infarction bears some risk.

General Conclusions

High dose intravenous short-time infusion of streptokinase can be performed safely in patients with evolving myocardial infarction. In the majority of cases, patency of coronary occlusion can be reestablished, or in thrombotically subtotal occlusion sufficient coronary blood flow can be restored. Preliminary experience suggests a beneficial effect on left ventricular function and ultimate infarct size.

Even though an absolute deadline for effective reperfusion may not be predicted in the individual case, it can be assumed that maximal benefit will be obtained by the earliest possible restoration of sufficient coronary blood flow. In comparison with intracoronary streptokinase application, coronary thrombus lysis time lasts somewhat longer with the intravenous approach. However, this may be balanced, at least in part, by a shorter delay when treatment is instituted without preceding coronary angiography. If immediate intracoronary streptokinase infusion cannot be performed, a high dose, short-time intravenous infusion of streptokinase appears to be the appropriate alternative. Of note is the European Cooperative Study Group trial (19), demonstrating a significantly lower 6 month mortality in patients treated with an intravenous streptokinase infusion up to 12 hours after the beginning of acute myocardial infarction. Of further note is the finding of improvement in left ventricular function in patients recanalized by intracoronary streptokinase infusion more than 8 hours after symptom onset (44,45). To ascertain the true impact of either intracoronary or intravenous streptokinase infusion on short- or long-term morbidity and mortality consequential to acute myocardial infarction, conclusive randomized trials are needed (25).

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